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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/357,349	07/14/1999	STEFAN LEO JOZEF MASURE	36813.3	9100

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GREENBERG TRAURIG, LLP
ONE INTERNATIONAL PLACE, 20th FL
ATTN: PATENT ADMINISTRATOR
BOSTON, MA 02110

EXAMINER	
TURNER, SHARON L	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 05/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/357,349	MASURE, STEFAN LEO JOZEF	
	Examiner	Art Unit	
	Sharon L. Turner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-9,17,18,24,41,44,58 and 59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-9,17,18,24,41,44,58 and 59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Response to Amendment

1. The amendments filed on 11-17-04 and 3-1-05 have been entered into the record and have been fully considered.

2. The declaration under 37 CFR 1.131(a) of Stefan Masure filed 11-17-04 is ineffective to over come any rejection. The declaration is not executed.

3. The request to amend inventorship under 37 CFR 1.48(b) is effective. The inventorship has been corrected.

4. Applicants request for Interference pursuant to 37 CFR 41.202 is noted. The request is held in abeyance until determination of patentability.

5. Claims 7-9, 17-18, 24, 41, 44 and 58-59 are pending.

Election/Restriction

6. Applicant's election of Group I, claims 7-9 (polypeptide of SEQ ID NO:3) in Paper No. 19 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

7. In the amendment of 11-17-04 the claims are substantially amended including with reference to SEQ ID NO's 4, 6, 7, 9, and 10. The claims however are written generically with respect to a functional equivalent derivative thereof. Accordingly, claims 7-9, 17-18, 24, 41, 44 and 58-59 will be examined.

8. SEQ ID NO:4 is under examination as being suitably related in structure. In particular, SEQ ID NO:3 is a 113 amino acid segment completely shared within SEQ ID NO:4. In particular SEQ ID NO:3 corresponds to residues 27-139 of SEQ ID NO:4.

SEQ ID NO:4 is longer and provides the Pro domain of Enovin. The relationship of SEQ ID NO's 6, 7, 9 and 10 is not clarified with respect to any structural similarity or basis to SEQ ID NO:3 or 4.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claim 7-9, 24, 41, and 44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection pertains to new matter. With respect to claim 8, there is no further support for the selection of 90% homology to these molecules. Further with respect to recitations of SEQ ID NO:9 and 10, support is not found within the earliest priority document, UK9815283.8.

Applicant's amendment of 11-17-04 introduces the new language "a functional equivalent derivative thereof" to claims 7-9, 24, and 44. This recitation differs from the specification, priority documents and notably from claims 17-18 reciting "a functional equivalent, derivative or bioprecursor thereof," alternatively. As recited, claims 7-9, 24, 44 appear to be drawn to a new sub-genus of molecules that are "functional equivalent derivaties thereof" without noted support. Accordingly the recitations constitute new matter.

Applicant's amendment of 11-17-04 also notes claim 41 drawn to "85% sequence identity with amino acid sequences of 3, 4, 6, 7, 9 or 10." Support is not found for "85% sequence identity with amino acid sequences of 3, 4, 6, 7, 9 or 10." Accordingly the recitations constitute new matter.

11. Claims 7-9, 17-18, 24, 41, 44 and 58-59 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection pertains to written description.

The specification describes a polypeptide sequence corresponding to precursor and mature forms of enovin designated as SEQ ID NO's 3 and 4, respectively that are noted to provide for neurotrophic activity. However, the claims as written include polypeptides comprising fragments and homologues, encompass polypeptides that vary substantially in length and also in amino acid composition as encompassed by the language, "a functional equivalent derivative thereof" (claims 7-9, 24, and 44), "a functional equivalend, derivative or bioprecursor thereof" (claims 17-18, 58-59), "derivative(s) (having) at least 90% homology" (claim 8) and "polypeptide(s) (having) at least 85% sequence identity" (claim 41) as recited. The instant disclosure of a single polypeptide, that of SEQ ID NO's:3-4 with the instantly disclosed specific activities, does not adequately support the scope of the claimed genus, which encompass a substantial variety of subgenera. A genus claim may be supported by a representative number of

species as set forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), which states:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention". Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1980) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.") Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d 1565, 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id at 1170, 25 USPQ2d at 1606."

A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus.

The instant specification discloses, however, a single isolated polypeptide sequence SEQ ID NO: 3-4. While the specification notes related prior art peptides

GDNF, NTN, and PSP which are neurotrophic such molecules are outside the scope of 85 and 90%, although they may be considered to be functional equivalents, derivatives or bioprecursors thereof as generically claimed. Yet, even so, the relationship is based solely on homology considerations.

Receptor function, however, cannot be reliably predicted from protein sequence homology. For example, Transforming Growth Factor (TGF-beta) Family members are inclusive of the noted family of neurotropic factors. OP-1 and OP-2 have notably been isolated as neurotrophins under particular conditions. Nevertheless, the genus is variable in both structures and functions. For example, OP-1 induces metanephrongenesis whereas closely related TGF-beta family members-BMP-2 and TGF-beta1-have no effect on metanephrogenesis under identical conditions (Vukicevic et al., 1996, PNAS USA 93:9021-9026). Platelet-derived Growth Factor (PDGF) Family VEGF, a member of the PDGF family, is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells while PDGF is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (Tischer et al., U.S. Patent 5,194,596, column 2, line 46 to column 3, line 2). Finally, vertebrate growth hormone of 198 amino acids becomes an antagonist (inhibitor of growth) when a single amino acid is changed (Kopchick et al, U.S. Patent No. 5,350,836). Even 99% homology does allow predictability in this instance.

Given the unpredictability of homology comparisons, and the fact that the specification fails to provide objective evidence that the additional sequences encompassed other than prior art GDNF, NTN, and PSP are indeed species of the

claimed genus as directed to neurotrophic activity, it cannot be established that the sub-genus of molecules now recited outside of those members as encompassed by 90% and 85% homology/identity considerations, is a representative number of species have been disclosed to support the genus claim.

12. Claims 7-9, 17-18, 24, 41, 44 and 58-59 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NO's:3 and 4, does not reasonably provide enablement for SEQ ID NO's, 6, 7, 9, 10, functional equivalent derivatives thereof, functional equivalents, derivatives or bioprecursors therof, 85% or 90% homology/sequence identity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification is insufficient to enable one skilled in the art to practice the invention as broadly claimed without undue experimentation. The factors relevant to this discussion include the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims.

Applicants claims are directed to peptides with greater than single amino acid substitutions, including naturally and non-naturally occurring variants, biologically active or functional equivalents, derivatives or bioprecursors thereof that are different functionally related peptides as differently directed to neurotrophic growth factors or specifically human neurotrophic growth factors.

The specification does not enable the broad scope of the claims which

encompasses a multitude of analogs or equivalents because the specification does not teach which residues can or should be modified such that requisite functionality is maintained, or that the noted growth factor is of "human" origin. The specification provides essentially no guidance as to which of the essentially infinite possible choices is likely to be successful in any particular use and the skilled artisan would not expect functional conservation amongst homologous sequences. Thus, applicants have not provided sufficient guidance to enable one skilled in the art to make and use the claimed derivatives in a manner reasonably correlated with the scope of the claims.

As to "90%" and "85%" variants, the skilled artisan recognizes that nucleic and amino acid alterations may lead to differences in function. For example, the skilled artisan recognizes as noted in Skolnick et al., Trends in Bioscience 18(1):34-39, 2000 and as further exemplified by Choh, PNAS 77(6):3211-14, 1990, that one or more amino acid deletions, insertions or substitutions including truncations results in unpredictable effects in the resulting biological molecule, its' biological function, the ability to bind and/or exhibit similar immunoreactivity. The specification teaches no structural or functional variant molecules within the scope of human sequences that are evidenced to be functional equivalent derivatives thereof, functional equivalents, derivatives or bioprecursosrs therof having neurotrophic acitivity. The specification fails to teach any residues which may be exchanged while retaining requsite activity or function and fail to teach the significance or function of any particular variants. As noted above the peptide structures and their pertinent sequences are insufficiently disclosed and/or enabled to the full scope of the claim.

Receptor function cannot be reliably predicted from protein sequence homology. For example, Transforming Growth Factor (TGF-beta) Family members are inclusive of the noted family of neurotropic factors. OP-1 and OP-2 have notably been isolated as neurotrophins under particular conditions. Nevertheless, the genus is variable in both structures and functions. A substantial portion of TGF-beta peptides share similar homology yet do not share neurotrophic activity. Instead they exhibit separate functions. For example, OP-1 induces metanephrongenesis whereas closely related TGF-beta family members-BMP-2 and TGF-beta1-have no effect on metanephrogenesis under identical conditions (Vukicevic et al., 1996, PNAS USA 93:9021-9026). Platelet-derived Growth Factor (PDGF) Family VEGF, a member of the PDGF family, is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells while PDGF is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (Tischer et al., U.S. Patent 5,194,596, column 2, line 46 to column 3, line 2). Finally, vertebrate growth hormone of 198 amino acids becomes an antagonist (inhibitor of growth) when a single amino acid is changed (Kopchick et al, U.S. Patent No. 5,350,836). Even 99% homology does allow predictability in this instance.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int.

1986). Thus, the skilled artisan cannot readily make and use the claimed sequences without further undue experimentation.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

14. Claims 7-9, 17-18, 24, 41, 44 and 58-59 are rejected under 35 U.S.C. 102(e) as being anticipated by Johansen et al., US Patent No. 6.593.133, July 15, 2003.

Johansen et al., teach Neublastin neurotrophic factors corresponding with 100 % similarity to instant SEQ ID NO:4, see in particular Johansen et al., SEQ ID NO:10. As noted in Johansen the peptide comprises a Pro domain which is cleaved to the mature form as disclosed in SEQ ID NO:12. Hence, instant SEQ ID NO:3, corresponding to residues 27-139 of SEQ ID NO:4 is anticipated by Johansen SEQ ID NO:12. The Patent notes human and non-human sequences and variants as well as pharmaceutical compositions, see in particular columns 9-11, and 18-22 in particular. Thus, the reference teachings anticipate the claimed invention, see in particular sequence listing, claims and columns 5-6.

15. Claims 7-9, 17-18, 24, 41, 44 and 58-59 are rejected under 35 U.S.C. 102(e) as

being anticipated by Milbrandt et al., US Patent No. 6,284,540, September 4, 2001.

Milbrandt et al., teach Artemin neurotrophic factors corresponding with 100 % similarity to instant SEQ ID NO:4, see in particular Milbrandt et al., SEQ ID NO:5. As noted in Milbrandt the peptide comprises a Pro domain which is cleaved to the mature form as disclosed in SEQ ID NO:3. Hence, instant SEQ ID NO:3, corresponding to residues 27-139 of SEQ ID NO:4 is anticipated by Johansen SEQ ID NO:3. The Patent notes human and non-human sequences and variants as well as pharmaceutical compositions, see in particular columns 10-17 and 22-23 in particular. Thus, the reference teachings anticipate the claimed invention, see in particular sequence listing, claims and columns 4-6.

16. Claims 7, 17-18 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Lin et al., Science, 260:1 130-1302, May 1993.

Lin et al., teach human GDNF precursor which shares 28% similarity with instant SEQ ID NO:3 and 4 and is a functional equivalent as the peptide enhances the survival, neurite outgrowth and differentiation of dopnminergic neurons, see in particular, Abstract. The peptide is in suitable pharmaceutical composition with diluent, carrier or excipient as denoted in solution, see in particular culture media noting function of the trophic factor to cells. Thus, the reference teachings anticipate the claimed invention.

17. Claims 7, 17-18 and 24 are rejected under 35 U.S.C. 102(e) as being anticipated by Johnson et al., US Patent 5,747,655 filed Nov. 1, 1996 and issued May 5, 1998.

Johnson et al., teach neurturin peptide which shares 38.6% sequence similarity with instant SEQ ID NOs:3 and 4 and thus is a functional equivalent derivative thereof, a

functional equivalent, derivative or bioprecursor of instantly claimed enovin of SEQ ID NOs:3 and 4. The peptide is a neuronal growth factor which supports the survival and outgrowth (neurite extension) of superior cervical ganglion neurons, see in particular Figures 3 and 4. The patent particularly denotes human and mouse neurotrophic factors, as well as pharmaceutical compositions, see in particular abstract, columns 6-20 and claims. Thus, the reference teachings anticipate the claimed invention.

Status of Claims

18. No claims are allowed.

19. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

20. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (571) 272-0894. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached at (571) 272-0887.

Sharon L. Turner, Ph.D.
May 16, 2005

SHARON TURNER, PH.D.
PRIMARY EXAMINER
3-16-05